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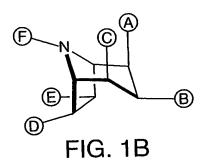
Our Ref. No. 5673-66690

For: HAPTEN-CARRIER CONJUGATES FOR USE IN DRUG-ABUSE THERAPY
AND METHODS FOR PREPARATION OF SAME
121 SW Salmon Street, Suite 1600

Portland, Oregon 97204

Telephone: 503/226-7391 Express Mail Label EV339203081, mailed: August 22, 2003

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William D. Noonan, M.D. Klarquist Sparkman, LLP Our Ker. No. 20/2-00090 Klarquist Sparkman, LLP
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Variables

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ಬ 0	Q	Q = H, OH, CH ₂ , HALOGEN, COOH, CARRIER
<i>3</i> 0	l d	PROTEIN, MODIFIED CARRIER PROTEIN
CJ 1	(CH ₂) _n Q	Q = H, COOH, HALOGEN, 2-NITRO-4-SULFOPHENYL ESTER, N-OXYSUCCINIMIDYL ESTER, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN, CJ 1.2
CJ 1.1	CO ₂ Q	$Q = H, CH_3$
CJ 1.2	COQ	Q = H, HALOGEN, 1-OXY-2-NITRO-4-SULFOPHENYL, N-OXYSUCCINIMIDYL, N-MALEIMIDYL, CARRIER PROTEIN, CJ 10
CJ 2	OCO(CH₂)"Q	Q = COOH, HALOGEN, 2-NITRO-4-SULFOPHENYL ESTER, N-OXYSUCCINIMIDYL ESTER, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 2.1	OCOCH=Q	Q = H
CJ 2.2	OCOCH(O)CH ₂	
CJ 2.3	OCO(CH ₂) _n CH(O)CH ₂	
CJ 3	CO(CH ₂),COQ	Q = H, OH, HALOGEN, 1-OXY-2-NITRO-4- SULFOPHENYL, N-OXYSUCCINIMIDYL, N-MALEIMIDYL, CARRIER PROTEIN, CJ 10
CJ 3.1	CO(CH ₂) _n CNQ	Q = OCH ₃ or CARRIER PROTEIN
CJ 4	OCO(CH ₂),COQ	Q = H, OH, HALOGEN, 1-OXY-2-NITRO-4- SULFOPHENYL, N-OXYSUCCINIMIDYL, N-MALEIMIDYL, CARRIER PROTEIN, CJ 10
CJ 4.1	CO(CH ₂) _n CNQ	$Q = OCH_3$ or CARRIER PROTEIN
CJ 5	CH2OCO(CH2),COQ	Q = H, OH, HALOGEN, 1-OXY-2-NITRO-4- SULFOPHENYL, N-OXYSUCCINIMIDYL, N-MALEIMIDYL, CARRIER PROTEIN, CJ 10
CJ 5.1	CO(CH ₂) _n CNQ	$Q = OCH_3$ or CARRIER PROTEIN
CJ 6	CONH(CH₂),Q	Q = H, COOH, HALOGEN, 2-NITRO-4-SULFOPHENYL ESTER, N-OXYSUCCINIMIDYL ESTER, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 7	Y(CH ₂),Q	Y = S, O, NH; Q = HALOGEN, COOH, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 7.1	CH₂Y(CH₂),Q	Y = S, O, NH; $Q = HALOGEN$, COOH, CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 8	OCOCH(OH)CH₂Q	Q = CARRIER PROTEIN, MODIFIED CARRIER PROTEIN
CJ 8.1	OCO(CH ₂),CH(OH)CH ₂ Q	Q = CARRIER PROTEIN, MODIFIED CARRIER PROTEI
CJ 9	OCOC ₆ H ₅	
CJ 11	YCO(CH ₂) _n COQ	Y = S, O, NH; Q = OH, CARRIER PROTEIN, MODIFIE CARRIER PROTEIN or HALOGEN

FIG. 2A

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ALTERNATIVE REPRESENTATION FOR SELECTED BRANCHES

$$-\text{CON(C)OCH}_2\text{CHO'} \equiv \begin{array}{c} O \\ O \\ C)O \end{array} \qquad \begin{array}{c} \text{(WHEREIN Q' IS A MODIFIED PROTEIN)} \\ \text{CJ10} \qquad CJ10 \end{array}$$

$$-\text{OCOCH(O)CH}_2 \equiv \begin{array}{c} O \\ O \\ CJ2.2 \end{array} \qquad \begin{array}{c} O \\ CJ2.2 \end{array}$$

$$-\text{OCO(CH}_2)_n\text{CH(O)CH}_2 \equiv \begin{array}{c} O \\ O \\ CJ2.3 \end{array} \qquad \begin{array}{c} O \\ CJ2.3 \end{array}$$

$$-\text{OCOC}_6\text{H}_5 \equiv \begin{array}{c} O \\ O \\ CJ9 \end{array}$$

FIG. 2B

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		BRANCHES	HES			u	LL
	-	A	В	اد	2		
ă.	PS:2	CJ1.1 WHERE Q=CH ₃	CJ2 WHERE Q= HALOGEN OR MODIFIED T CELL EPITOPE CONTAINING	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
Δ.	PS-3	CJ1.1 WHERE Q=CH ₃	CARMIER AND 11-1 CJO WHERE Q= MODIFIED T CELL EPITOPE CONTAINING	CJO WHERE Q=H	CJ0 WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
	PS-4	CJ1.1 WHERE Q=CH ₃	CJ4 WHERE Q= MODIFIED T CELL EPITOPE CONTAINING	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
	PS-5	CJ1.1 WHERE	CARRIEH AND 11=1 CJ9	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ3 WHERE Q=CARRIER PROTEIN, n=2
<u> </u>		CJ5 WHERE O=CARRIER PROTFIN AND	6FO	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
		CJ1.2 WHERE	670	CJO WHERE	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
	8-0 1		CJ2 WHERE	CJO WHERE	CJO WHERE	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
<u>- </u>	PS-10		15 WH		HERE		CJ1 WHERE
<u>т</u>	PS-11	CJ6 WHENE Q=H OR CL1.1 WHENE Q=CH ₃		OSO WARNE Q=H	H=0	H=0	+
	PS-12	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH ₃		CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
_ _ _ 문	ECUS	PRECUSORS/CONJUGATES		FIG. 3B(1)			

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										— Т				\neg
	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1	C.11 WHERE	O=H, n=1	CJ1 WHERE Q=H, n=1	CJ1 WHERE	Q=H, n=1		CJ1 WHERE Q=H, n=1	O 11 WHERE	O=H, n=1	2	3
	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	ממח/אי פי ט	OJO WHENE	CJO WHERE Q=H		T=O		CJO WHERE Q=H	_	CJO WHENE Q=H		H=0
	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	+		CJO WHERE Q=H	O WHERE	H=0		CJO WHERE Q=H		CJO WHERE Q=H		020 WHEN 0=H
	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE CJO WHERE CJO WHERE		CJO WHERE Q=H	CJO WHERE Q=H				CJO WHERE Q=H		CJO WHERE Q=H		CJO WHENE Q=H
	ZOOF!	CARRIER AND N=2 CJ2.2	CJ8		CJ2.3	CJ8.1		CJ4	CI 1 WHERE Q=COOH,	HALOGEN, 2-NITRO SULFOPHENYL ESTE OXYSUCCINIMIDYL E CARRIER PROTEIN	MODIFIED CARRIER	CJ7		െ
BRANCHES	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH3	CJ6 WHERE Q=H OR CJ1.1	WHERE Q=CH ₃ CJ6 WHERE O=H OR CJ1.1	WHERE Q=CH ₃	CJ6 WHERE Q=H OR CJ1.1	CJ6 WHERE	WHERE Q=CH ₃	CJ6 WHERE Q=H OR CJ1.1	WHERE CECTS	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH ₃		CJ6 WHERE Q=H OR CJ1.1	WHERE Q=CH ₃	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH ₃
	PS-13	P.S-14			PS-16	DC. 17		PS-18		PS-19		PS-20		PS-21

PRECUSORS/CONJUGATES

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		BRANC	NCHES		\vdash		
<u> </u>	00-Sd	CJ6 WHERE Q=H OR CJ1.1	673	CJO WHERE	CJO WHERE	CJO WHERE	CJ1 WHENE Q=CJ 1.2
		WHERE Q=CH ₃	0	CJO WHERE	CJO WHERE	CJO WHERE	CJ1 WHERE
u.	PS-23	cho.	80 0	+	CJO WHERE	CJO WHERE	CJ1 WHERE
<u>u</u> _	PS-24	CJ7.1	8PO		ממון אין פו פ	O IO WHERE	C.11 WHERE
<u> </u>	ps.25	CJ7	6FO	CJO WHERE	CJO WHENE O=H	AU AH-D	H=O
	96.00	C.11.2	6CO	CJO WHERE	CJO WHERE	CJO WHERE	CSJ WHENE
	PS-27	CJ6 WHERE Q=H OR CJ1.1	673	CJ2	CJO WHERE	CJO WHERE	CJ1 WHERE Q=H, n=1
		WHERE C=CH ₃					
	PS-28	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH ₃	C 9	COL1 WHERE COOH HALOGEN SULPOPHENYL SUCCINIMIDYL SUCCINIMIDYL ESTER, CARRIER PROTEIN, MODI- FIED T CELL EP- ITOPE CONTAIN- ING CARRIER, OJ.2	CJO WHERE	CJO WHERE	CJ1 WHERE Q=H, n=1
		L			חס חנייאי סייס	O WHERE	
	PS-29	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH3	ോ	CJ2.2		H-O	
	PS-30		ero	CJ8	CJO WHERE	CJO WHERE	CJ1 WHERE Q=H, n=1
					C IO WHERE	C.IO WHERE	CJ1 WHERE
	PS-31	Q=H OR CJ1.1 WHERE Q=CH ₃	സ	CJ2.3	H=0	H=Q	Q=H, n=1
—д П	RECUS	PRECUSORS/CONJUGATES		FIG. 3B(3)			

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ָּהַ ה ה	1 = 1 = 1 = 1 = 1 = 1 = 1 = 1 = 1 = 1 =	ERE	n=1	### ###	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1	
	Q=WnEne Q=H, n=1	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1	CJ1 WHERE Q=H, n=1					
	CJO WHENE O=H	CJO WHERE Q=H	CJ0 WHERE Q=H	CJ0 WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	
-	CJ0 WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJ2	CL1 WHERE Q= COOH, HALOGEN 2-NITRO-4- SULFOPHENYL ESTER, N-OXY- SUCCINIMIDYL ESTER, CARRIER PROTEIN, MODI- FIED T CELL EP- ITOPE CONTAIN- ING CARRIER, CJ1.2	CJ2.2	CJB	E.SLO	3(4)
	CJ8.1	CJ4	CJS	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	CJO WHERE Q=H	FIG. 3B(4)
HES	ോ	603	6F2 .	CJ9	CJ9	CJ9	6FO	673	S
BRANCHE	CJ6 WHERE Q=H OR CJ1.1	CJ6 WHERE Q=H OR CJ1.1	CJ6 WHERE Q=H OR CJ1.1	CJ6 WHERE Q=H OR CJ1.1	CJ6 WHERE Q=H OR CJ1.1 WHERE Q=CH ₃	CJ6 WHERE Q=H OR CL1.1	WHERE Q=CH ₃ CJ6 WHERE Q=H OR CL1.1	WHERE Q=CH ₃ CJ6 WHERE Q=H Q=H CL1.1	
	PS-32	PS-33	PS-34	PS-35	PS-36	PS-37	PS-38	PS-39	PRECUS

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	BRANCHES	HES				ממוח/אי דו כ
950 H-10	CJ6 WHERE Q=H OR CJ1.1	CJ9	CJO WHERE Q=H	CJ8.1	CJ0 WHERE Q=H	Q=H, n=1
	WHERE CECH3 CJ6 WHERE C=H OR CJ1.1	673	CJO WHERE Q=H	CJ4	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
\$\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	WHERE Q=CH ₃ CJ6 WHERE Q=H OR CJ1.1	CJ9	CJO WHERE Q=H	CJ5	CJO WHERE Q=H	CJ1 WHERE Q=H, n=1
₹ \ <u>Q @</u>	WHERE G=CH ₃ CJ6 WHERE Q=H OR CJ1.1	CJ9	CJO WHERE Q=H	CJO WHERE Q=H	CJ2	CJ1 WHERE Q=H, n=1
	CJ6 WHERE Q=CH ₃ CJ6 WHERE WHERE Q=CH ₃	670	CJO WHERE Q=H	CJ0 WHERE Q=H	CL1 WHERE Q= COOH, HALOGEN 2-NITRO-4- SULFOPHENYL ESTER, N-OXY- SUCCINIMIDYL ESTER, CARRIER PROTEIN, MODI- FIED T CELL EP- ITOPE CONTAIN- ING CARRIER, CJ1.2	CJ1 WHERE Q=H, n=1
18	PRECUSORS/CONJUGATES	w.				

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	CHUNDA	SH H				
DC.45	CJ6 WHE O=H OR C	CJ9	CJO WHERE Q=H	CJO WHERE Q=H	CJ2.2	CJ1 WHERE Q=H, n=1
) 	WHERE Q=CH ₃					O 14 WHERE
PS-46	CJ6 WHERE Q=H OR CJ1.1	673	CJO WHERE Q=H	CJO WHERE Q= Q=H	CJ8	Q=H, n=1
!) 						C 1 WHERE
PS-47	l	വേ	CJO WHERE Q=H	CJO WHERE Q=H	CJ2.3	Q=H, n=1
:) -	WHERE Q=CH ₃					C.11 WHERE
00.48	CJ6 WHERE O=H OR CJ1.1	6°C)	CJO WHERE Q=H	CJO WHERE Q=H	CJ8.1	O=H, n=1
						C.11 WHERE
07.00	OJEW POH-O	ഗോ	CJO WHERE Q=H	CJO WHERE Q=H	CJ4	Q=H, n=1
) 						C 11 WHERE
PS-50	1	6FO	CJO WHERE Q=H	CJO WHERE Q=H	CJS	Q=H, n=1
5 - -	WHERE Q=CH ₃					
PRECU	PRECUSORS/CONJUGATES	S				
			FIG 38/6)	(6		

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				-	ŧ	1
		a	C	_	ע	
	A	ום		101	ט יא אורובטב	O 14 WHERE
COCAINE	CJ1.1	ൈ	H H	H H	- H-O	Q=H, n=1
	WHERE		I J	ב וו כ	- Î	•
	Q=CH3			7071	Handwor O	C.11 WHERE
ECOGONINE	CJ1.1	CJ10 WHERE CJ0 WHERE	CJ0 WHERE	CJO WHERE Q=H	050 H=Q	Q=H, n=1
METHYL	WHERE	3	i S		,	
בים בים	CITO II			7071 241 61 6	O IO WILERE	C. IO WHERE
NORCOCAINE	CJ1.1	₆ ට	CJO WHERE	CJO WHENE	H=0	H=Q
	WHERE		<u></u>	<u> </u>	· }	
	Q=CH3				חמשואי טו ט	C.II WHERE
BENZOYL	റാ	ൊ	CJO WHERE	CJO WHERE	H=0	Q=H, n=1
ECGONINE	WHERE		3	- 1 3	\$	
i)	H000=0					

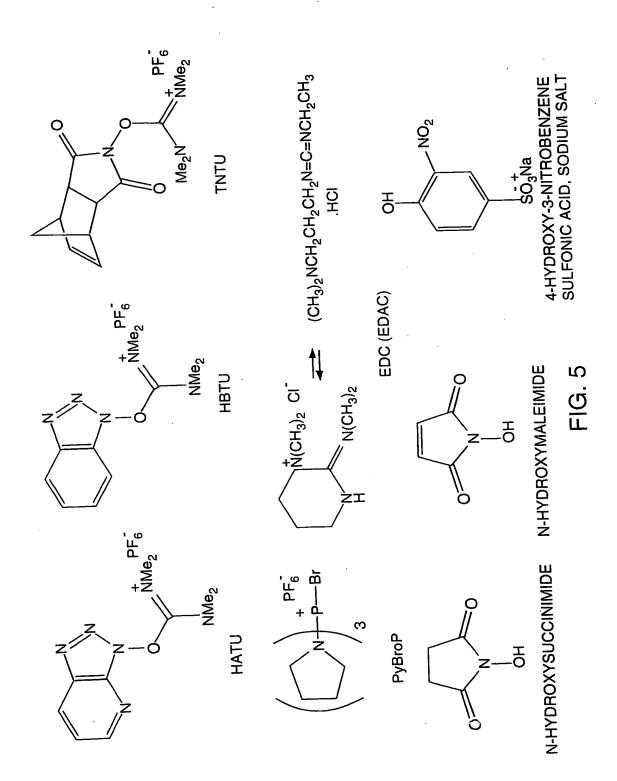
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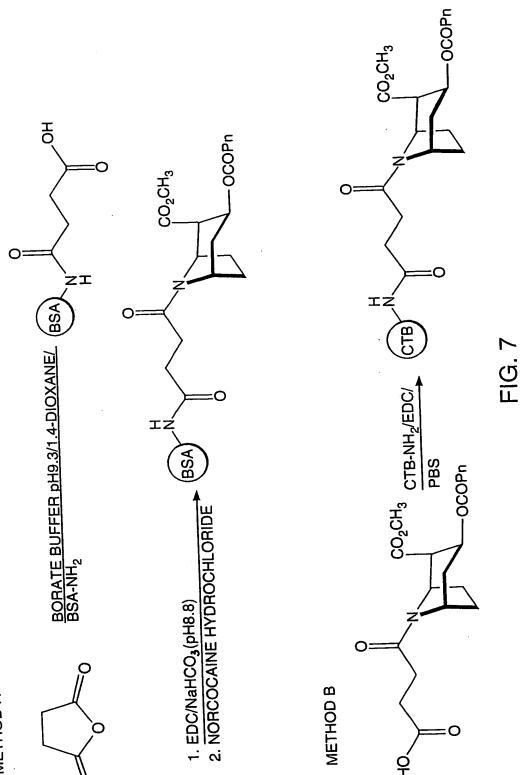
NICOTINE

OTHER COMMONLY ABUSED DRUGS

AcO. NCH₃ AcO nin DIAZEPAM **HEROIN**

FIG. 6

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METHOD A

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WHERE Q = CI,
$$NO_2$$
 NO_2 NO_3

FIG. 8

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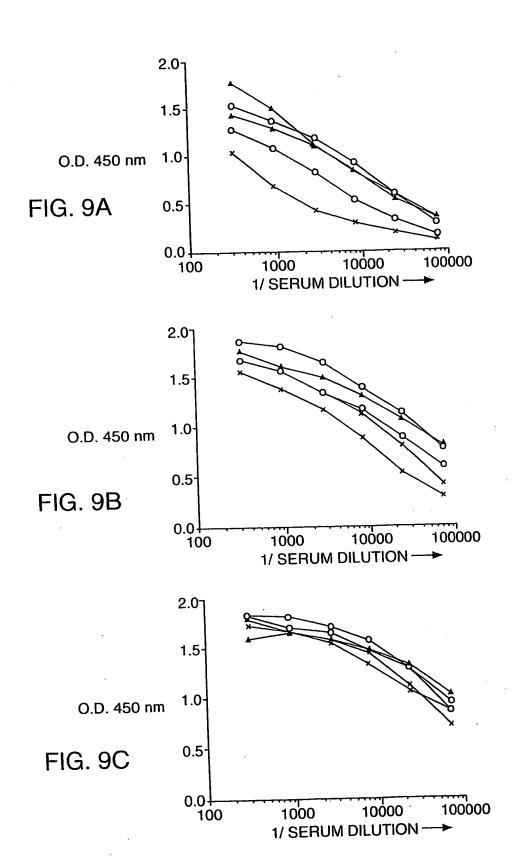
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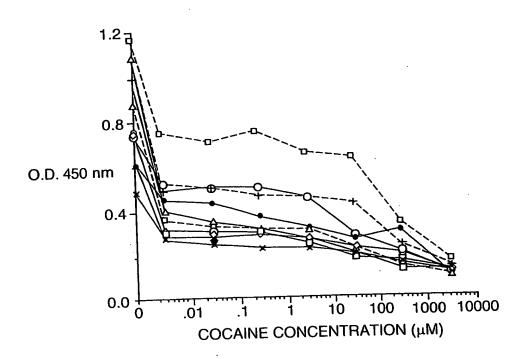


FIG. 10A

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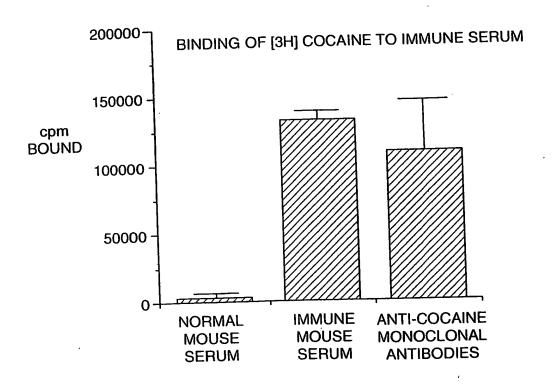


FIG. 10B

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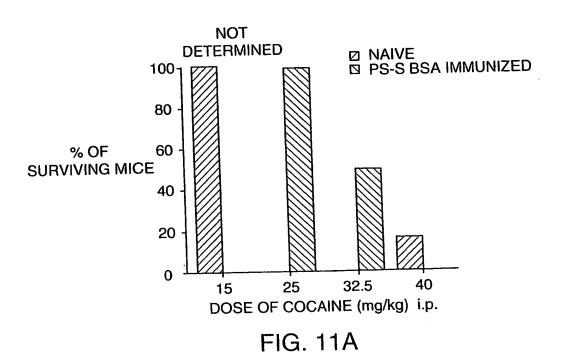
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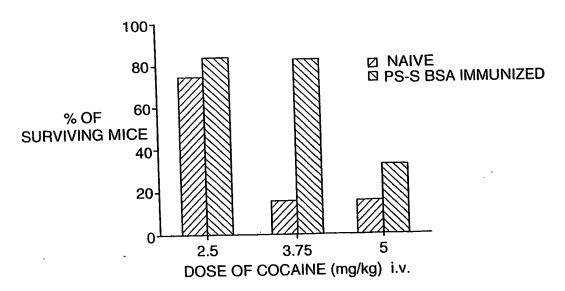


FIG. 11B

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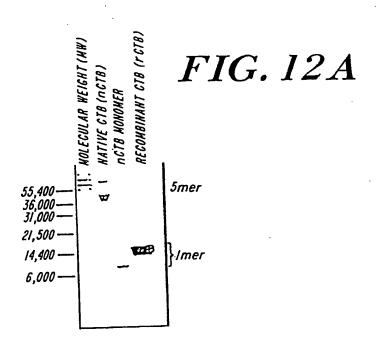
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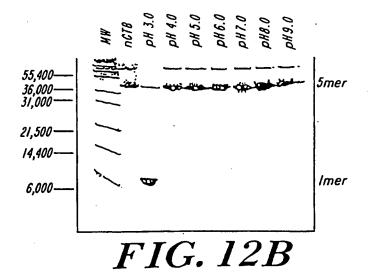
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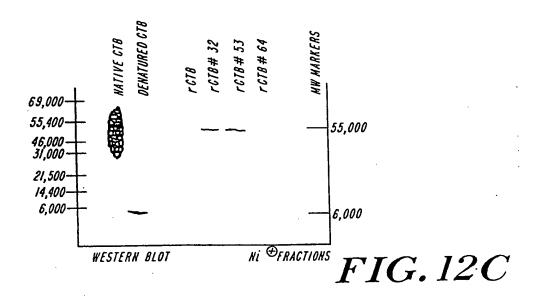
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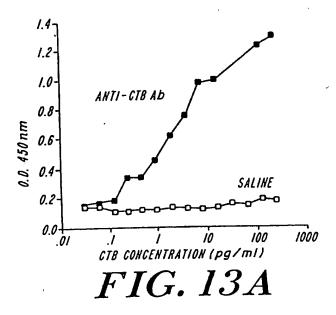
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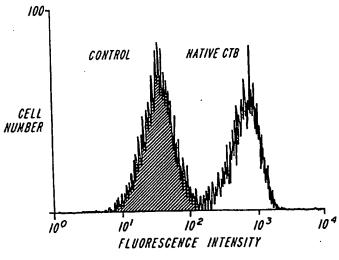


FIG. 13B

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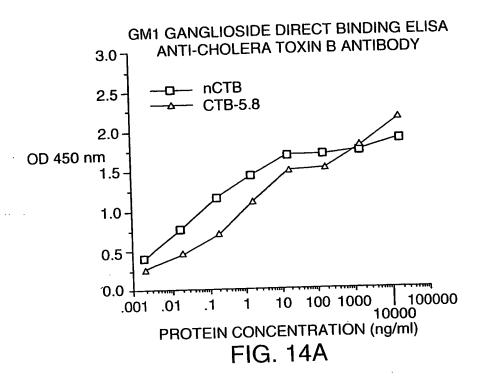
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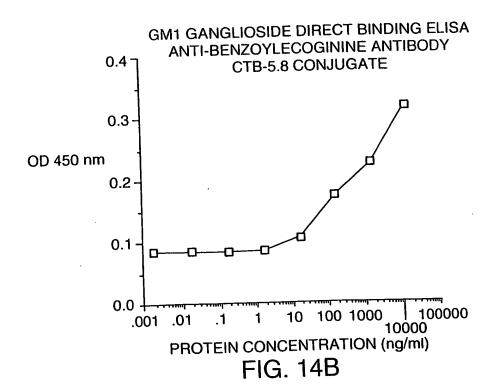
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FIG. 15

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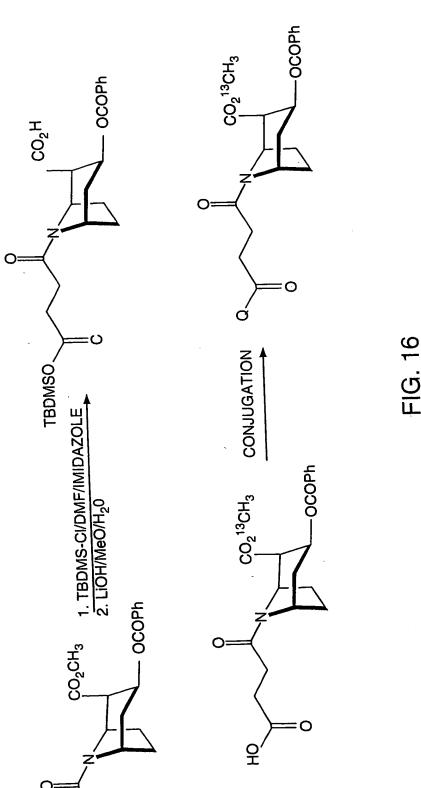
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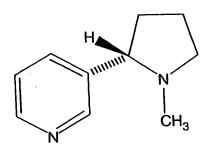


FIG. 17A

FIG. 17B

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F	CJ0 where Q=CH ₃		CJ0 where Q=CH ₃	C.10 where Q=CH ₃		CJ3 where Q=OH or T-cell epitope containing carrier, n=2	CJ0 where Q=CH ₃	CJ0 where Q=CH ₃	CJ0 where Q=CH ₃
ч			1			:	CJI where Q=H or a T-cell epitope containing carrier n=3	CJI where Q=H or a T-cell epitope containing carrier n=4	CJI where Q=H or a T-cell epitope containing carrier n=5
		CJO where Q=H	CJO where Q=H		CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H
	اد	CJO where Q=H	CJO where Q=H		CJ1 where $Q=COOH$ or where $Q=CJ1.2$, wherein $Q=T-cell$ epitope containing	CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H
	В	CJO where Q=H	CJI where Q=COOH or where Q=CJ1.2; wherein Q=T-cell	epitope containing carrier.	CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H
	4	CJ1 where Q=COOH or wherein Q=CJ1.2, wherein Q=T-cell epitope containing	carrier. CJO where Q=H		CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H	CJO where Q=H
		PS-51	PS-52		PS-53	PS-54	PS-55	PS-56	PS-57

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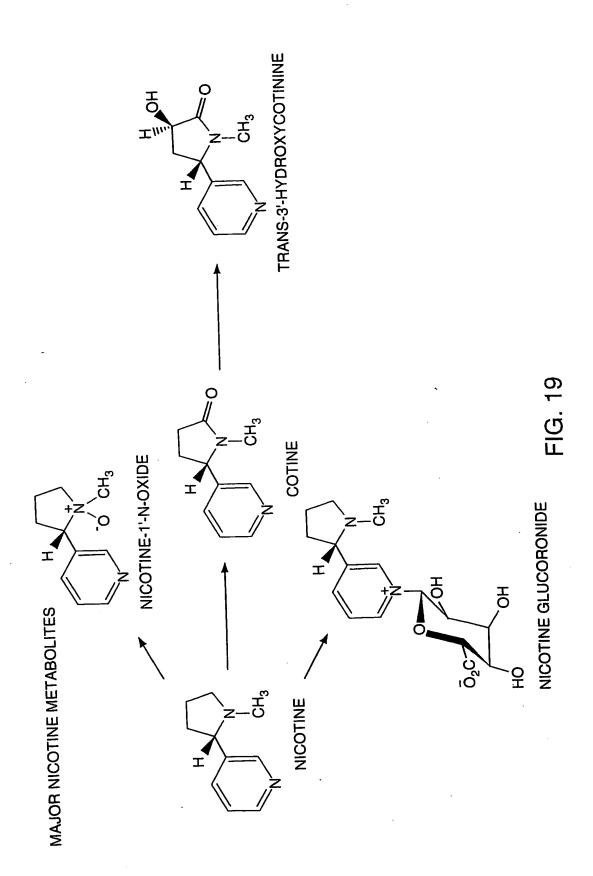
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				. Ē	хрге	ss M	ail	Lal	pel E	V3:	3920	030
14		CJ0 where Q=CH ₃		CJ0 where Q=CH ₃				CJO where Q=CH ₃				
<u> </u>	į	CJ1 where $Q=H$ or a	T-cell epitope containing carrier n=7					,				
	2	CIO where O=H		H - O croth 010	CJU Wilere (4-n			H=0 expers OLD				
	ပ	H = 0 0204 010	CJO Wilere G-IT		CJO where Q=H			77 0 27 070	CJU wnere ਪ≕⊓		•	
	В		CJO where Q=H		CJO where Q=H				CJ11 where Y=NH	Q=OH Of 1-cell	carrier	Carro
			CJO where Q=H		CJ11 where Y=NH	Q=OH or 1-cell	epitope containing	carrier	CJO where Q=H			
			PS-58		PS-59				PS-40			

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FIG. 20

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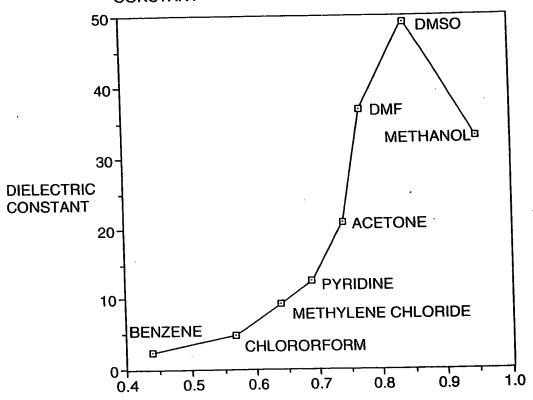
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RATIO OF SUCCINYLATED NORCOCAINE ISOMERS AS A FUNCTION OF SOLVENT DIELECTRIC CONSTANT



RATIO OF TWO ISOMERIC FORMS

FIG. 21

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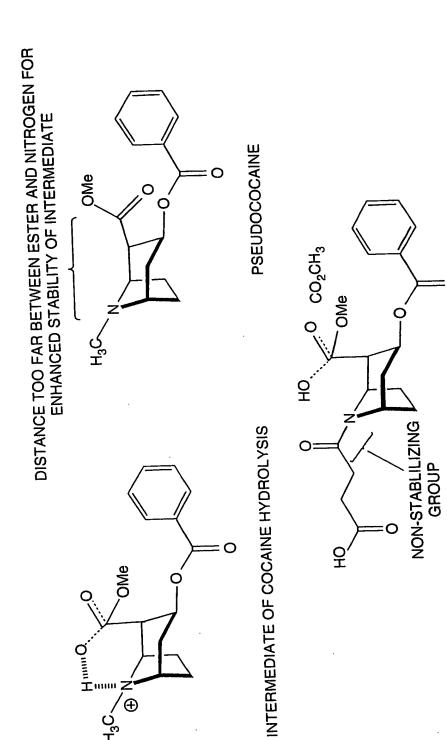
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HYDROLYZED SUCCINYLATED NORCOCAINE INTERMEDIATE

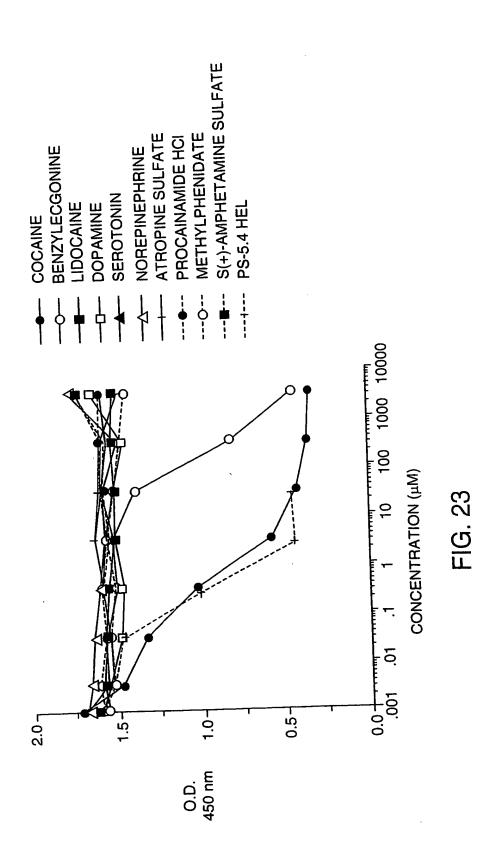
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STRONG ANTIBODY RESPONSES INDUCE BY NICOTINE-BSA CONJUGATE

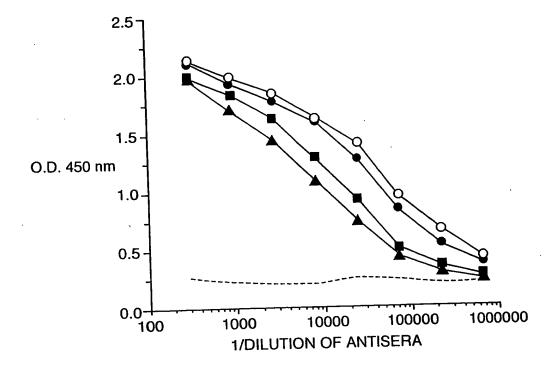


FIG. 24

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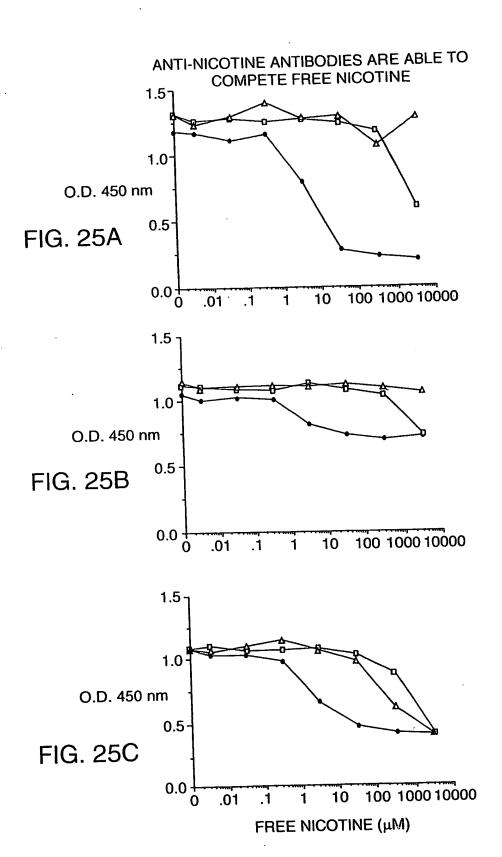
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Production of anti-cocaine antibodies in Wistar rats

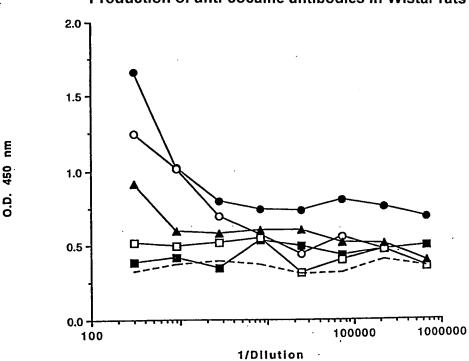


FIG.26

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ANTI-COCAINE ANTIBODIES GENERATED IN WISTAR RATS ARE ABLE TO BIND FREE COCAINE

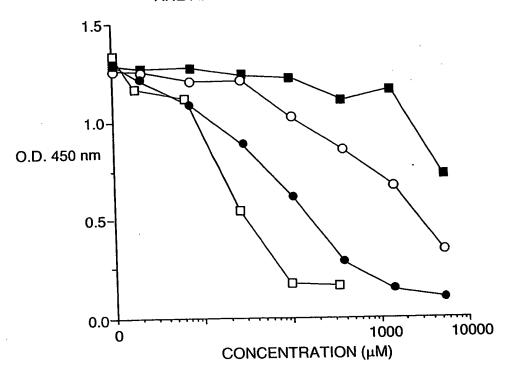


FIG. 27